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Therapeutic Class Review
Carbidopa/levodopa/entacapone (Stalevo®)

Overview/Summary

Stalevo® is a combination antiparkinsonian medication that is composed of levodopa, carbidopa, and entacapone. It was approved by the Food and Drug Administration (FDA) on June 11th, 2003. Of the three components that comprise Stalevo® the combination levodopa/carbidopa is available generically.[1-3] Stalevo® is currently approved for the treatment of idiopathic Parkinson's disease as a substitute for patients who are currently being treated with the individual components. It is also indicated as replacement therapy for patients who are currently on immediate-release levodopa/carbidopa therapy without entacapone treatment and who begin experiencing signs and symptoms of end-dose wearing-off effect.[3]

Parkinson's disease is characterized by a lack of dopamine in the corpus striatum region of the brain. Levodopa is the chemical precursor to dopamine and effectively crosses the blood-brain barrier where it is converted to dopamine and causes improvement of Parkinson's symptoms. When administered orally levodopa is rapidly converted to dopamine in the extracerebral tissue and only a small portion of active dopamine is transported to the brain. Carbidopa inhibits the conversion of levodopa to dopamine in the peripheral tissues allowing more levodopa to be transferred to the brain. The coadministration of levodopa and carbidopa effectively increases the half-life of levodopa from 50 minutes to 1.7 hours and allows for the use of smaller amounts of levodopa doses to produce the desired effect on the patients symptoms. Entacapone is a selective and reversible catechol-O-methyltransferase (COMT) inhibitor. When the action of levodopa conversion to dopamine is inhibited by carbidopa, COMT becomes the primary metabolizing enzyme. By administering entacapone concurrently with levodopa/carbidopa, plasma levels of levodopa are greater and more sustained. This greater sustainment of levels results in a more constant dopaminergic stimulation in the brain leading to greater effects on the signs and symptoms of Parkinson's disease.[3]

Based on the current literature, the addition of entacapone to the levodopa/carbidopa combination produces the greatest efficacy in patients that have developed motor fluctuations due to prolonged levodopa use. Clinical trials have demonstrated that patients with the early form of the disease who lacked motor fluctuations, benefited from Stalevo® in quality of life parameters but not in the reduction of motor symptoms. In contrast patients who had developed motor fluctuations experienced improvement in their motor symptoms when compared to levodopa/carbidopa only therapy.[4-8]

An overview of the currently available Parkinson's disease guidelines indicates that there is no overall agreement between the guidelines as to which is the preferred agent for initial treatment. However the guidelines are in agreement that levodopa produces the most efficacious relief of Parkinson's symptoms.

The National Institute for Health and Clinical Excellence (NICE) guidelines state that there are no universal first-choice agents for patients with early or late Parkinson's disease. They recommend that levodopa can be used in patients with early Parkinson's disease; however the dose should be kept as low as possible in order to minimize the development of motor complications. They also recommended that in later Parkinson's disease entacapone can be used to help decrease motor fluctuations. If entacapone is selected the NICE guidelines recommend the use of Stalevo® as the combination medication of choice.[9] The American Academy of Neurology guidelines state that levodopa is the most effective of all drugs for symptoms of Parkinson's disease. The guidelines also discuss that clinical trials have shown that early use of levodopa therapy might predispose patients to develop long-term motor complications such as

wearing-off and dyskinesia. Their recommendation is that patients who require symptomatic treatment can be started on anticholinergic therapy or selegiline prior to the administration of dopaminergic treatment. When selecting the appropriate dopaminergic treatment either levodopa or dopamine agonists are appropriate. However the treatment choice is dependent on the impact of improving motor disability which is better improved by levodopa, and the lessening of motor complications which is better with dopamine agonists.[10-11]

The European Federation of Neurological Societies guidelines state that levodopa is the most effective symptomatic antiparkinsonian drug available. The guidelines for early Parkinson's disease recommend that for younger patients with Parkinson's disease dopamine agonist should be initiated first, in order to prolong the use of levodopa and delay the development of motor complications. For the elderly, early use of levodopa is recommended as this patient population is less prone to developing motor complications.[12-13]

Medications

Table 1. Medications Included Within Class Review[1]

Generic Name (Trade name)	Medication Class	Generic Availability
Levodopa/carbidopa/entacapone (Stalevo®)	Dopamine Agonist and Catechol-O-methyltransferase (COMT) Inhibitor	-

Indications

Table 2. Food and Drug Administration Approved Indications[3]

Generic Name	Indication
Levodopa/ carbidopa/ entacapone	The treatment of idiopathic Parkinson's disease as a substitute for patients who are currently being treated with the combination carbidopa/levodopa and entacapone as separate products. It is also indicated as a replacement in patients who are currently being treated with immediate-release carbidopa/levodopa therapy without concurrent entacapone and begin experiencing signs and symptoms of end-dose wearing-off effect.

Pharmacokinetics

Table 3. Pharmacokinetics[1,3,14]

Generic Name	Bioavailability (%)	Metabolism	Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Levodopa/ carbidopa/ entacapone	Levodopa: 80-99 Carbidopa: 40-70 Entacapone: 35	Levodopa: liver, gut, kidney Carbidopa: liver Entacapone: liver (extensively metabolized)	Levodopa: Urine: 70-80 Carbidopa: Urine: 30 Entacapone: Urine: 10 Feces: 90	Levodopa: yes (dopamine) Carbidopa: no Entacapone: yes (cis-Isomer)	Levodopa: 1.7 hours Carbidopa: 1.6-2 hours Entacapone: 0.4-0.7 (β-phase) 2.4 (γ-phase)

Clinical Trials

A study by Fung et al was a randomized, double-blind, active-controlled, parallel-group study. It investigated whether treatment with levodopa/carbidopa and entacapone improved patients' quality of life greater than levodopa/carbidopa, in patients with no or minimal motor fluctuations. Patients were required

to be on three to four stable equal doses of levodopa/carbidopa and were randomized to receive either levodopa/carbidopa or levodopa/carbidopa and entacapone. The primary outcome measure was the change from baseline to week 12 in the total Parkinson's Disease Questionnaire (PDQ)-8 score. This questionnaire evaluated both motor and non-motor domains. The results of the study indicated that patients randomly assigned to the levodopa/carbidopa and entacapone treatment group showed a mean improvement in PDQ-8 of 0.8 point, whereas those assigned to the levodopa/carbidopa group showed a mean deterioration in PDQ-8 scores of 0.6 point. The difference between the two groups was statistically significant (P=0.021). However, upon further analysis of the PDQ-8 subgroups, it was shown that only the non-motor aspects of the questionnaire proved to be statistically significant. In respect to adverse events, 7.6% of patients discontinued the study. The most common adverse events were urine discoloration, nausea, dizziness, constipation, and diarrhea. The overall conclusions of the study demonstrated that the addition of entacapone in patients with no or minimal disabling motor fluctuations, predominantly improved the patients non-motor domains rather than their motor symptoms.[4]

A 26-week study by Olanow et al was a randomized, double-blind, placebo-controlled, parallel-group study. The study examined the efficacy and safety of the addition of entacapone in patients with idiopathic Parkinson's disease who were not exhibiting motor complications, and were being treated with levodopa/carbidopa. The primary efficacy endpoint of the study was the change from baseline to week 26 in the motor subscale portion (Part III) of the Unified Parkinson's Disease Rating Scale (UPDRS). Secondary endpoints included the measurement of quality of life through the use of the PDQ-39 questionnaire, the Short Form (SF)-36 and the Parkinson's Symptom Inventory (PSI) test. The results of the study indicated that the addition of entacapone did not improve motor scores in the UPDRS scores in patients who were not suffering from motor complications. There were improvements seen in several quality of life measurements, including portions of the PDQ-39, SF-36 and the PSI. Rates of adverse events were similar between both groups, with adverse events classified as mild. The results of the study indicate that patients who were not experiencing motor complications did not gain motor symptom relief from the addition of entacapone to their levodopa/carbidopa therapy.[5]

An open-label, multi-center study by Boiko et al evaluated the efficacy and safety of Stalevo® (levodopa/carbidopa/entacapone) in patients with Parkinson's disease who were experiencing motor fluctuations. Patients were taking levodopa/carbidopa combination products and were then switched to Stalevo® at the start of the study. At the end of the trial positive benefits of Stalevo® use were seen with a 29.2% reduction in the UPDRS score. The reductions were not limited to the total score, but also to the individual parts of the UPDRS test. All four subscales that were examined showed statistically significant reductions in test scores. Furthermore, 86.0% of the study population reported a decrease in their duration of off periods and 33.0% in the number of off periods. In general, fewer than 10% of patients reported adverse effects. This trial demonstrated that switching patients with motor fluctuations from levodopa/carbidopa to Stalevo® had high efficacy rates as well as minimal adverse effects.[6]

Koller et al was an open-label, multi-center, single-arm, 4-week investigation of Stalevo®. The primary aim of the study was to assess the safety and tolerability of a direct switch from an immediate release levodopa/carbidopa formulation to Stalevo® in patients who were experiencing wearing-off effects. At the study entry patients were switched from immediate release levodopa/carbidopa to an equivalent Stalevo® dose. The primary outcome of the study was intolerability, which was defined as the percentage of patients who discontinued the study due to adverse effects. The study found that 7.0% of patients discontinued the trial due to adverse events. Some common adverse events seen were nausea, dizziness, somnolence, discoloration of the urine and constipation. Efficacy was assessed as change from baseline in the UPDRS (Parts II, III, and II&III). The results demonstrated that there was a statistically significant improvement (P<0.001) across all parts of the UPDRS. Furthermore, investigators reported improvement in 68.1% of patients and 68.6% of patients self reported improvements. The study concluded that Stalevo® was well tolerated and provides clinical improvements in patients who were experiencing wearing-off symptoms.[7]

A study by Brooks et al was a 6-week open-label, parallel-group, active-control trial that examined the use of Stalevo® in patients with Parkinson's disease who were experiencing wearing-off effects with their

current levodopa/carbidopa therapy. Patients were switched to either Stalevo® or levodopa/carbidopa and entacapone as separate entitys. The primary efficacy measure was defined as the treatment success rate as assessed by the patient at week six of the study. At the end of the study, 73% of the patients treated with Stalevo® and 76% of those treated with levodopa/carbidopa and separate entacapone indicated they were in better clinical condition. No significant differences were seen in adverse events between the combination Stalevo® product and the separate levodopa/carbidopa and entacapone agents. The overall conclusions of the study were that Stalevo® was similar in both efficacy and safety as compared to separate levodopa/carbidopa and entacapone agents.[8]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fung et al[4] Levodopa/carbidopa and entacapone administered as separate entities vs levodopa/carbidopa Patients discontinued their commercial levodopa/ carbidopa preparation and commenced their blinded study drug at equivalent doses of levodopa/ carbidopa, with or without entacapone, on the day after baseline visit. Mean levodopa dose at baseline in the levodopa/ carbidopa and entacapone group was 395.2 mg and 420.0 mg for the levodopa/ carbidopa group.	AC, DB, MC, RCT Patients ≥30 years old with idiopathic Parkinson's disease, a modified Hoehn & Yahr stage of 1.0-2.5, and 0.0-3.0 hours of nondisabling off-time over a consecutive 48 hour period, were required to be taking 3-4 stable equal doses of levodopa/carbidopa with a total daily levodopa dose of 300-800 mg/day for at least 1 month before study entry	N=184 12 weeks	Primary: Change from baseline to week 12 in the total PDQ-8 score Secondary: Change from baseline to week 4 and week 12 in: UPDRS parts I,II,III and IV subscale scores, UPDRS parts I-III combined, number of wearing-off symptoms, proportion of patients experiencing wearing-off using the Wearing-Off Card and safety	Primary: The levodopa/carbidopa and entacapone treatment group had a mean improvement in their PDQ-8 scores of 0.8 point. The levodopa/carbidopa group had a mean deterioration in the PDQ-8 of 0.6 point. The 1.4 point difference between the two groups was found to be statistically significant (*P*=0.021). A subgroup analysis of the individual PDQ-8 questions showed that the treatment difference favored the levodopa/carbidopa and entacapone treatment group and was statistically significant in questions: • #3: Depression (*P*=0.025) • #4: Close personal relationships (*P*=0.037) • #6: Communication (*P*=0.007) • #8: Social stigma (*P*=0.033) Secondary: The mean UPDRS part II scores improved in the levodopa/ carbidopa and entacapone group but not in the levodopa/ carbidopa group. The difference was not statistically significant at week 4 (*P*=0.057) but did reach significance by week 12 (*P*=0.032). The difference in part III results between the two treatment groups did not achieve statistical significance (*P*=0.087). Parts I and IV had very low baseline scores and did not demonstrate a significant change over the 12 week treatment period (*P* values not reported). The combined UPDRS parts I-III scores improved in both treatment groups at week 4 and 12. However the difference between the two treatment groups did not reach significance at week 4 (*P*=0.071), but did at week 12 (*P*=0.047). The mean number of wearing-off symptoms across all patients at baseline was 4.4 and this was reduced to 3.1 at week 12. There was no significant difference in the reduction of wearing-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				off symptoms between the two groups (*P* values not reported). Patients in levodopa/carbidopa and entacapone treatment group who experienced at least one wearing-off symptom was 78.5% at baseline and decreased to 69.8% and 61.8% at weeks 4 and 12 respectively. Patients in the levodopa/carbidopa group had an 84.6% at baseline and this decreased to 61.5% at both weeks 4 and weeks 12. There was no statistically significant difference between the two groups (*P* values not reported). Both of the treatment regimens were safe and well tolerated over the study period. Adverse events attributed to the discontinuation of the study in 14 patients (7.6%). In the levodopa/carbidopa and entacapone treatment group 66% of patients had at least one adverse event and this number was 56% in the levodopa and carbidopa group. The most common adverse events were: • Urine discoloration: (23% levodopa/carbidopa and entacapone vs 6% levodopa/carbidopa) • Nausea: (12% levodopa/carbidopa and entacapone vs 8% levodopa/carbidopa) • Dizziness: (5% levodopa/carbidopa and entacapone vs 7% levodopa/carbidopa) • Constipation: (5% levodopa/carbidopa and entacapone vs 3% levodopa/carbidopa) • Diarrhea: (5% levodopa/carbidopa and entacapone vs 4% levodopa/carbidopa)
Olanow et al[5] Levodopa/carbidopa and entacapone 200 mg administered as separate entities vs	DB, MC, PC, PG, RCT Patients were male or female ≥30 years older with idiopathic Parkinson's disease, had at least two of the following: rigidity,	N=750 26 weeks	Primary: Change from baseline to week 26 in the motor subscale score of the UPDRS	Primary: Change from baseline in the motor subscale score of the UPDRS to week 26 was -0.9 for the entacapone group and -0.8 for the placebo group. This change was not statistically significant (*P*=0.83). Secondary: Changes from baseline in the ADL subscale score was -0.1 for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results

levodopa/carbidopa and placebo administered as separate entities
 	
Mean levodopa dose at baseline in the entacapone group was 401 mg and 406 mg for the placebo group.
	resting tremor, and bradykinesia; doses of levodopa had to be stable for one month prior to study initiation		Secondary:
			Change from baseline to week 26 in: ADL subscale scores of the UPDRS, total UPDRS score, PDQ-39, SF-36, PSI, need for supplemental dopaminergic therapy and safety
				the entacapone group and 0.2 for the placebo group. The difference between the two groups was not significant (*P*=0.16).
				
				Changes from baseline in the total UPDRS score was -0.9 for the entacapone group and -0.4 in the placebo group. The difference between the groups was not significant (*P*=0.42).
				
				Changes in the PDQ-39 scores were -0.7 in the entacapone group and 1.6 in the placebo group with the difference between these results reaching statistical significance (*P*<0.001).
				
				Statistically significant differences in the SF-36 scores were seen for the subsections of:
				• Physical functioning (*P*=0.047):
				  ○ Entacapone Change Score: -0.1
				  ○ Placebo Change Score: -0.2
				• Vitality domain (*P*=0.04):
				  ○ Entacapone Change Score: -0.0
				  ○ Placebo Change Score: -0.1
				• Physical component (*P*=0.009):
				  ○ Entacapone Change Score: -0.6
				  ○ Placebo Change Score: -1.9
				
				Frequency and distress measures of the PSI test had significant improvements in the entacapone group
				• Frequency (*P*=0.007):
				  ○ Entacapone Change Score: -1.5
				  ○ Placebo Change Score: 0.2
				• Distress Change Score (*P*=0.02):
				  ○ Entacapone Change Score: -1.4
				  ○ Placebo Change Score: 0.3
				
				More patients in the placebo group (12.5%) required an increase in levodopa dose than did the entacapone group (8.0%; *P*=0.046).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Seven patients died during the course of the study. None of their deaths were attributed to the study medication. Nausea and dyskinesia were the most common observed adverse events. The rate of nausea was 18.2% in the entacapone group and 11.7% in the placebo group. For dyskinesia 12.6% in the entacapone group and 10.9% in the placebo group.
Boiko et al[6] Levodopa/DCI at a dose up to 750 mg/day administered as a combination product vs levodopa/carbidopa/ entacapone 200 mg administered as a combination product Dose determined according to patients daily levodopa dose taken prior to start of study.	MC, OL Patients with idiopathic Parkinson's disease with motor fluctuations (wearing-off of the effects of single levodopa dose, and experiencing on-off phenomenon)	N=50 6 weeks	Primary: Change from baseline at week 6 in UPDRS scores Secondary: Safety	Primary: By week 6, treatment with levodopa/carbidopa/ entacapone was shown to cause a 29.2% reduction in the overall UPDRS score. Subscale scores of the UPDRS indicated the following: • A decrease in the UPDRS score of mental functions from 3.6 to 2.5 (P<0.0001). • Activities of daily living scores improved from a score of 14.3 to 10.7 (P<0.0001). • Motor impairments improved from a score of 24.2 to 19.4 (P<0.0001). • The complications of treatment score decrease from 4.0 to 3.3 (P<0.001). Secondary: Less than 10% of patients reported nausea, orthostatic reactions and headache. None of the adverse effects warranted corrective treatment.
Koller et al[7] Levodopa/carbidopa 25/100 mg (1/2 tablet, 1 tablet, 1 ½ tablet) administered as a combination product vs levodopa/carbidopa/	MC, OL Male and female patients ≥30 years old with idiopathic Parkinson's disease and exhibiting at least two out of three symptoms (rigidity, resting tremor,	N=169 4 weeks	Primary: The percent of patients who discontinued the study due to adverse events Secondary: The percent of subjects	Primary: Seven percent of patients in the study withdrew due to adverse events. Common adverse events listed were nausea, continued or worsening off-periods, dizziness and discoloration of the urine. Secondary: Of the entire patient population 8.5% of patients who did not have dyskinesia at the onset of the study developed it, and 43.6% experienced a worsening of their already existing

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
entacapone administered as a combination product Dose of combination levodopa/carbidopa/ entacapone based on patient's dose of levodopa/carbidopa prior to start of study.	bradykinesia) and who were experiencing wearing-off with or without mild dyskinesia		experiencing new onset dyskinesia and worsening of pre-existing dyskinesia, change from baseline in the UPDRS (Parts II,III, and II&III), change from baseline in UPDRS question-39, change from baseline on the PDQ-39 total score and investigators and patient clinical assessments	dyskinesia symptoms. UPDRS scores improved significantly in all parts and their values were as follows: • Part II: 1.7 reduction from baseline (*P*<0.001) • Part III: 3.9 reduction from baseline (*P*<0.001) • Parts II & III: 5.6 reduction from baseline (*P*<0.001) • Question 39: 0.3 reduction from baseline (*P*<0.001) PDQ-39 scores also improved significantly with a reduction in baseline of 4.0 (*P*<0.001). Investigators and patients noted improvement in treatment. At the end of the study investigators noted some degree of improvement in 68.1% of patients. 68.6% of patients also reported improvements.
Brooks et al[8] Levodopa/carbidopa and entacapone 200 mg administered as separate entities vs levodopa/carbidopa/ entacapone 200 mg administered as a combination product Patients in the combination levodopa/carbidopa/ entacapone arm received an equal amount of levodopa that was used during the 2	AC, MC, PG, OL, RCT Male and female patients with a mean age of 65 with idiopathic Parkinson's disease, were required to have end-of-dose wearing-off for at least 1 year prior to study entry, as well as answered "Yes" to at least one question in the 7-point MFQ, all patients were also required to have Hoehn and Yahr staging of 1 to 3	N=177 10 weeks 2 week run-in period, 6 week treatment period, 2 week follow-up period	Primary: Treatment success rate assessed by the patient at week 6 as evaluated by the 7-point CGI-C Secondary: Treatment success rate assessed by the investigators at week 6 as evaluated by: 7-point CGI-C, change in MFQ scores from baseline, change in UPDRS Part III score from baseline and safety	Primary: At week 6, 73% of the patients in the combination product treatment group and 76% in the separate entity group indicated they were in better clinical condition (*P* values not reported). Secondary: According to the investigators 79% of patients in both the combination product treatment group and the separate entity group were in better clinical condition (*P* values not reported). At week 6 motor fluctuations were reduced from baseline falling from 100% of cases to 64% in the combination product group and 73% in the separate entity group (*P* values not reported). In the combination product group 87% of patients and 81% of the patients in the separate entity group reported improved responses on the MFQ (*P* values not reported). At week 6 the UPDRS scores were significantly improved from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
week run-in period for 6 weeks.				baseline in both the combination product group (*P*<0.001) and the separate entity group (*P*=0.0016). Adverse events were reported in 55% of the total patient population and resulted in 5% of the patients discontinuing from the study. The most common adverse events seen were nausea, diarrhea, dyskinesia, abnormal urine, dizziness, influenza-like symptoms, back pain and insomnia. There was no significant difference in the adverse events between the two treatment groups (*P* values not reported).

Study abbreviations: AC=active-controlled, DB=double-blind, DCI=dopa decarboxylase inhibitor, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
Miscellaneous abbreviations: ADL=activities of daily living, CGI-C=Clinical Global Impression of Change, MFQ=Motor Fluctuation Questionnaire, PDQ-8=Parkinson's Disease Questionnaire, PSI=Parkinson's Symptom Inventory, SF=short form, UPDRS=Unified Parkinson's Disease Rating Scale

Special Populations[1,3,14]

Table 5. Special Populations

Generic Name	Population and Precaution				
	Elderly/ Children	Renal dysfunction	Hepatic dysfunction	Pregnancy Category	Excreted in Breast Milk
Levodopa/ carbidopa/ entacapone	Safety and efficacy not established in pediatric patients. Dose adjustments are not indicated in otherwise healthy elderly parkinsonian patients.	No dose adjustment necessary. Use with caution in patients with severe renal disease.	Use with caution in patients with hepatic impairment.	C	Unknown

Adverse Drug Events

Frequencies for the levodopa/carbidopa adverse events were not reported, but were similar to those seen with entacapone use. In general the most common adverse events seen with the use of Stalevo® are dyskinesia, nausea, diarrhea and urine discoloration.

Table 6. Adverse Drug Events [3,15]

Adverse Event	Generic Name	Reported Frequency (%)
Abdominal pain	entacapone	8
Constipation	entacapone	6
Diarrhea	entacapone	10
Dizziness	entacapone	8
Dyskinesia	entacapone	25
	levodopa/carbidopa	✔
Fatigue	entacapone	6
Hyperkinesia	entacapone	10
Hypokinesia	entacapone	9
Loss of appetite	levodopa/carbidopa	✔
Nausea	entacapone	14
	levodopa/carbidopa	✔
Urine discoloration	entacapone	10
Vomiting	levodopa/carbidopa	✔

✔ Percent not reported.

Contraindications / Precaution[1,3]

Contraindications to Stalevo® include: hypersensitivity to any of the three individual components, the use of a nonselective monoamine oxidase (MAO)-inhibitor therapy with or within 14 days of use, narrow-angle glaucoma, undiagnosed skin lesions, or a history of melanoma. Stalevo® has the potential for causing mental disturbances. Therefore all patients should be monitored for the development of depression or suicidal tendencies. Furthermore, all patients with a history of psychoses should be treated with caution. Stalevo® should be administered cautiously in patients with severe cardiovascular or pulmonary disease, bronchial asthma or endocrine disease. In patients with a history of myocardial infarctions, cardiac function should be monitored carefully during the initial dosing adjustment period. The medication also has the potential to cause upper gastrointestinal hemorrhaging in patients with a history of peptic ulcers, and caution should be used when administering the medication to this patient population. Caution is also required when reducing Stalevo® doses or discontinuing the medication as periodic cases of a symptom complex resembling neuroleptic malignant syndrome have been reported in patients with levodopa/carbidopa dose reduction or cessation of therapy. Patients with wide-angle glaucoma should

use Stalevo® cautiously and their intraocular pressure should be monitored carefully for any changes. Hallucinations have also been associated with dopaminergic therapy, as have cases of rhabdomyolysis and fibrotic complications such as retroperitoneal fibrosis or pleural effusion.

Drug Interactions

Table 7. Drug Interactions[3]

Generic Name	Interacting Medication or Disease	Potential Result
Levodopa/ carbidopa/ entacapone	Anti-hypertensive agents	Symptomatic postural hypotension may occur. Dosage adjustment of antihypertensive drug may be required.
Levodopa/ carbidopa/ entacapone	Dopamine D_2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone and isoniazid)	Therapeutic effects of levodopa may be reduced.
Levodopa/ carbidopa/ entacapone	Iron salts	May reduce bioavailability of carbidopa, levodopa, entacapone.
Levodopa/ carbidopa/ entacapone	Metoclopramide	May increase bioavailability of levodopa. May affect disease control by its dopamine receptor antagonistic properties.
Levodopa/ carbidopa/ entacapone	Monoamine oxidase (MAO) inhibitors	Concomitant therapy with selegiline may be associated with severe orthostatic hypotension.
Levodopa/ carbidopa/ entacapone	Phenytoin	Beneficial effects of levodopa may be reversed. Patients should be observed.
Levodopa/ carbidopa/ entacapone	Tricyclic antidepressants	Rare reports of adverse reactions such as hypertension and dyskinesia.

Dosage and Administration

Table 8. Dosing and Administration[1,3,15]

Generic Name	Adult Dose	Pediatric Dose	Availability
Levodopa/ carbidopa/ entacapone	Transferring patients from separate carbidopa/levodopa and entacapone preparations to Stalevo®: Patients can be directly switched to the corresponding strength of Stalevo® containing equal amounts of carbidopa/levodopa. Transferring patients to Stalevo who are not being treated with entacapone and who are being treated with greater than 600 mg of levodopa per day: Levodopa dose reduction may be required when adding entacapone to therapy. Titrate dose using individual	Safety and efficacy in children have not been established.	Tablet (carbidopa/levodopa/ entacapone): 50: 12.5/50.0/200.0 mg 75: 18.75/75.00/200.00 mg 100: 25/100/200 mg 125: 31.25/125.00/200.00 mg 150: 37.5/150.0/200.0 mg 200: 50/200/200 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	carbidopa/levodopa and entacapone 200 mg, and then transfer to Stalevo® once stabilized. Transferring patients to Stalevo® who are not being treated with entacapone and who are being treated with less than 600 mg of levodopa per day: Can be transfer to corresponding dose of Stalevo®		

Potential Advantages

- Combination entity allows for a decrease in pill burden.
- Incidence of adverse events similar to levodopa/carbidopa.
- Effective in alleviating symptoms due to motor fluctuations (ie. wearing off and on-off phenomenon.

Potential Disadvantages/Unanswered Questions

- Due to the combination product only being available as a brand name product cost is a potential limitation of Stalevo®.
- No increase in effectiveness over conventional levodopa/carbidopa therapy in those patients who have not yet developed motor fluctuations.

Clinical Guidelines

According to the National Institute for Health and Clinical Excellence (NICE) there is no universal first-choice therapy for patients with Parkinson's disease.[9] Levodopa, dopamine agonists and monoamine oxidase-B (MAO-B) inhibitors may all be used in patients with early Parkinson's disease for symptomatic treatment. The MAO-B inhibitors are considered more convenient compared to the other agents due to ease of administration and may be considered in patients who need symptomatic treatment prior to the administration of dopaminergic therapy. Anticholinergics should be limited to younger patients with early Parkinson's disease associated with severe tremor. In elderly patients, early use of levodopa is recommended as they are less prone to developing motor complications but more sensitive to neuropsychiatric adverse events.

In addition, there is no single agent of choice for late stage Parkinson's disease.[9] Levodopa, dopamine agonists, MAO-B inhibitors and catechol-O-methyl transferase (COMT) inhibitors may all be considered to reduce motor fluctuations in patients with late stage Parkinson's disease. For the symptomatic control of wearing-off in late, complicated Parkinson's disease, several strategies have been recommended. Such strategies include increasing the dosing frequency of levodopa or switching to a controlled-release formulation of the medication. Also adding a COMT-inhibitor, MAO-B inhibitor or dopamine agonist as adjunctive therapy is also recommended. If these strategies fail it is recommended that amantadine or an anticholinergic be considered. For the symptomatic control of dyskinesias in late, complicated Parkinson's disease the addition of amantadine is recommended. Other strategies include reducing the dose size of levodopa or discontinuing or reducing the dose of MAO-B inhibitors or COMT inhibitors, however these strategies increase the risk of worsening off-time.

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
National Institute for Health and Clinical Excellence (NICE): **Parkinson's Disease: Diagnosis and**	• There is no universal first-choice therapy for patients with Parkinson disease (PD). Clinical and lifestyle characteristics of the patient should be taken into account. • Levodopa may be used in patients with early PD for symptomatic treatment with doses kept as low as possible to reduce the development

Clinical Guideline	Recommendations
Management in Primary and Secondary Care (2006)[9]	of motor complications. • Dopamine agonists may be used in patients with early PD for symptomatic treatment. Dopamine agonists should be titrated to a clinically efficacious dose and another agent in the class maybe used if the patient fails therapy or side effects prevents titration. • Monoamine oxidase-B (MAO-B) inhibitors may be used in patients with early PD for symptomatic treatment. • Beta-blockers may be used for symptomatic treatment of selected people with postural tremor, but are not considered first-line agents. • Amantadine may be used in patients with early PD, but is not considered a first-line agent. • Anticholinergics may be used in young patients with early PD for symptomatic treatment associated with severe tremor. These agents are not considered first-line due to limited efficacy and the propensity to cause neuropsychiatric side effects. • Extended-release levodopa should not be used to delay the onset of motor complications in patients with early PD. • Most patients with PD will develop motor complications over time and will require levodopa therapy. Adjuvant medications have been developed to take concomitantly with levodopa to help reduce the motor complications and improve quality of life associated with late stage PD. • There is no single agent of choice for late stage PD. • Extended-release levodopa may help reduce motor complications in patients with late stage PD, but is not considered a first-line agent. • Dopamine agonists may be used to reduce motor fluctuations in patients with late stage PD. Dopamine agonists should be titrated to a clinically efficacious dose and another agent in the class maybe used if side effects prevent titration. • MAO-B inhibitors may be used to reduce motor fluctuations in patients with late stage PD. • Catechol-O-methyl transferase (COMT) inhibitors may be used to reduce motor fluctuations in patients with late stage PD. This class of medication is taken concomitantly with levodopa. • Amantadine may be used to reduce dyskinesias in patients with late stage PD. • "Drug holidays" should be avoided because of the risk of developing neuroleptic malignant syndrome.
American Academy of Neurology (AAN) Practice Parameter: **Initiation of Treatment for Parkinson's Disease: An Evidence Based Review (2002)[10]**	• Patients with PD, who require symptomatic treatment, may be started with selegiline prior to the administration of dopaminergic therapy. • Selegiline has mild symptomatic benefits in PD, and no convincing evidence of neuroprotective benefits. • Levodopa, cabergoline, ropinirole and pramipexole are effective in ameliorating motor complications and impairment in the activities of daily living (ADL) in patients with PD who require dopaminergic therapy. Of these agents, levodopa is more effective in treating motor complications and ADL disability and is associated with a higher incidence of dyskinesias than dopamine agonists. • Levodopa or a dopamine agonist may be initiated in patients with PD who require dopaminergic therapy. • Cabergoline, ropinirole and pramipexole resulted in fewer motor complications (i.e., wearing off, dyskinesias, on-off fluctuations) compared to levodopa.

Clinical Guideline	Recommendations
	• Treatment with a dopamine agonist was associated with more frequent adverse drug reactions (hallucinations, somnolence and edema in the lower extremities) than levodopa. • When initiating treatment with levodopa in patients with PD, either an immediate-release or sustained-release formulation may be used. In clinical trials, there was no difference in the rate of motor complications between the two formulations.
AAN Practice Parameter: **Treatment of Parkinson's Disease with Motor Fluctuations and Dyskinesia (2006)**[11]	• Rasagiline and entacapone demonstrated statistically significant reduction in off time as compared to placebo in clinical trials. It is recommended that these two agents should be offered to reduce off-time. • Pergolide demonstrated some improvement in the reduction in off-time as compared to placebo in clinical trials. However, a large number of patients on pergolide experienced more dyskinesias. Pramipexole demonstrated some reduction in off-time in placebo controlled trials. Ropinirole and tolcapone showed reduction in off-time compared to placebo. It is recommended that pergolide, pramipexole, ropinirole and tolcapone can be considered to reduce off-time. Due to side effects and the strength of the studies, entacapone and rasagiline are preferred over pergolide, pramipexole, ropinirole and tolcapone. • Apomorphine, cabergoline and selegiline were studied in clinical trials that lacked proper enrollment and methods to provide conclusive evidence of reducing off-time. It is recommended that these agents may be considered to reduce off-time. • Bromocriptine and extended-release carbidopa/levodopa do not help to reduce off-time. • Amantadine demonstrated reduction in dyskinesia compared to placebo in clinical trials. It is recommended that amantadine may be considered for patients with PD for reducing dyskinesias. • Deep brain stimulation of the subthalamic nucleus may be considered as a treatment option in PD patients to help improve motor function and to reduce motor fluctuations, dyskinesias and medication usage.
European Journal of Neurology: **Joint Task Force Report: European Federation of Neurological Societies/Movement Disorder Society; Early (Uncomplicated) Parkinson's Disease (2006)**[12]	• No adequate clinical trials have been conducted to provide definitive evidence for pharmacological neuroprotection. • In the management of early PD, MAO-B inhibitors have a modest benefit in treating the symptomatic complications of PD compared to levodopa and dopamine agonists. These agents are more convenient due to the ease of administration (i.e., one dose, once daily, no titration). • Amantadine and anticholinergics offer minimal symptom control compared to levodopa. • Anticholinergics are poorly tolerated in the elderly and use should be restricted to younger patients. • Levodopa is the most effective anti-Parkinson's drug for symptomatic relief. • Early use of levodopa in the elderly is recommended as they are less prone to developing motor complications but more sensitive to neuropsychiatric adverse events. • Pramipexole and ropinirole are effective dopamine agonists as monotherapy in the treatment of early stage PD. • Convincing evidence that older agents in the class are less effective than the newer non-ergot agents is lacking. • Dopamine agonists have a lower risk of developing motor complications than compared to levodopa. These agents do have a greater incidence of

Clinical Guideline	Recommendations
	adverse effects which include hallucinations, somnolence and edema in the lower extremities. • Younger patients should be started on a dopamine agonist as initial treatment to prolong the use of levodopa and the development of motor complications.
European Journal of Neurology: **Joint Task Force Report: European Federation of Neurological Societies/Movement Disorder Society; Late (Complicated) Parkinson's Disease (2006)**[13]	Symptomatic Control of Wearing-off • Adjusting the levodopa dose by increasing the dosing frequency has been beneficial to control off-time. • Switching from the standard formulation of levodopa to the controlled-release formulation improves wearing-off symptoms. • Adding a COMT-inhibitor or a MAO-B inhibitor is effective in reducing off-time by 1-1.5 hours/day. • Adding a dopamine agonist provides modest benefit. All dopamine agonists are equally effective and efficacious in reducing off-time. Pergolide and other ergot derivatives are reserved for second-line use, due to the adverse effect of valvulopathy. • Addition of amantadine or anticholinergics should be considered in patients with severe off symptoms who fail the recommended strategies listed above. Symptomatic Control of Dyskinesias • Patients may benefit for up to 8 months by adding amantadine 200-400 mg/day for the treatment of dyskinesias. • Reducing the dose size of levodopa has been beneficial in reducing dyskinesias. The risk of off-time increases but can be compensated by increasing the frequency of levodopa dosing. • Discontinuing or reducing the dose of MAO-B inhibitors or COMT inhibitors can help control dyskinesias, however the risk of worsening off-time increases. • The addition of clozapine or quetiapine has shown to be beneficial in reducing peak dose dyskinesia. Clozapine's adverse effect of agranulocytosis limits its use. • Deep brain stimulation of the subthalamic nucleus allows the reduction of dopaminergic treatment. • Apomorphine given as a continuous subcutaneous infusion under direct medical supervision allows for the reduction of levodopa therapy and helps control dyskinesias.

Conclusions

Stalevo® is a combination antiparkinsonian medication that consists of levodopa, carbidopa, and entacapone. The current clinical evidence suggests that Stalevo® is an effective medication for Parkinson's patients who are experiencing symptoms associated with motor fluctuations. In this patient population the medication improved both the patient's motor and quality of life symptoms. In patients with early Parkinson's that had not yet developed motor fluctuations Stalevo® did not appear to be any more efficacious than conventional levodopa/carbidopa therapy.

The current available clinical guidelines do not recommend a preferred agent in initiation of therapy. However there is agreement that of all current agents available, levodopa produces the greatest symptom efficacy. Long-term use of the medication however leads to motor complications. The National Institute for Health and Clinical Excellence (NICE) guidelines recommend that levodopa can be used in younger patients with Parkinson's disease; however the dose should be kept as low as possible in order to prevent early motor fluctuations. They also recommended that in later Parkinson's disease entacapone can be added to levodopa therapy to help decrease motor fluctuations. If entacapone is selected the NICE

guidelines recommend the use of Stalevo® as the combination medication of choice.[9] The American Academy of Neurology (AAN) guidelines recommend that patients who require symptomatic treatment can be started on anticholinergic therapy or selegiline prior to the administration of dopaminergic treatment levodopa is the most effective of all drugs for symptoms of Parkinson's disease. The guidelines also discuss that clinical trials have shown that early use of levodopa therapy might predispose patients to develop long-term motor complications such as wearing-off and dyskinesia.[10-11]

Recommendations

Based on the information presented in the review above and cost considerations, no changes are recommended to the current approval criteria.

Stalevo® is preferred on The Office of Vermont Health Access (OVHA) preferred drug list.

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